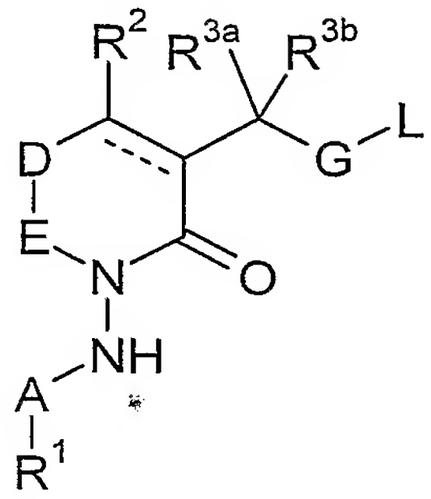
Claims

1. A compound of formula I



I

wherein

the dashed line is absent or represents a bond;

A represents C(O), $S(O)_2$, C(O)O (in which latter group the O moiety is attached to R^1), C(O)NH, $S(O)_2NH$ (in which latter two groups the NH moiety is attached to R^1) or C_{1-6} alkylene;

R^1 represents

(a) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, CN, C_{3-10} cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy and aryl), OR^{4a}, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, B^1-C(O)-B^2-R^{4i}, aryl and Het^1),

(b) C_{3-10} cycloalkyl or C_{4-10} cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo, =O, CN, C_{1-10} alkyl, C_{3-10} cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy and aryl), OR^{4a}, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, B^3-C(O)-B^4-R^{4i}, aryl and Het^2,

(c) aryl, or

(d) Het^3;

R^{4a} to R^{4i} independently represent, at each occurrence,

(a) H,

(b) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkoxy, aryl and Het^4),

(c) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, aryl and Het^5),

(d) aryl or

(e) Het^6,

provided that R^{4b} does not represent H when n is 1 or 2;

the group -D-E-

(a) when the dashed line represents a bond, represents $-C(R^{5a})=C(R^{5b})-$,

or

(b) when the dashed line is absent, represents $-C(R^{6a})(R^{6b})-C(R^{7a})(R^{7b})-$;

R^{5a} and R^{5b} independently represent H, halo, OH, C_{1-4} alkyl, $(CH_2)_{0-4}O(C_{1-3}$ alkyl) (which latter two groups are optionally substituted by one OH group or one or more F atoms);

R^{6a}, R^{6b}, R^{7a} and R^{7b} independently represent H, F or methyl;

or R^{5a} and R^{5b} together represent C_{2-4} *n*-alkylene;

or one of R^{6a} and R^{6b}, together with one of R^{7a} and R^{7b}, represents C_{1-4} *n*-alkylene;

R^2 represents

(a) H,

(b) halo;

(c) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, CN, C_{1-4} alkoxy, C(O)OH, C(O)O-C_{1-4} alkyl and OC(O)-C_{1-4} alkyl) or

(d) together with R^{3a}, R^2 represents C_{2-3} *n*-alkylene, T^1-(C_{1-2} *n*-alkylene) or (C_{1-2} *n*-alkylene)-T^1, which latter three groups are optionally substituted by halo, or

(e) together with R^{3a} and R^{3b}, R^2 represents T^2-[C(H)=], wherein T^2 is bonded to the C-atom to which the group R^2 is attached;

R^{3a} and R^{3b} independently represent H, F or methyl (which latter group is optionally substituted by one or more F atoms), or

(a) together with R^2, R^{3a} represents C_{2-3} *n*-alkylene, T^1-(C_{1-2} *n*-alkylene) or (C_{1-2} *n*-alkylene)-T^1, which latter three groups are optionally substituted by halo, or

(b) together with R^2, R^{3a} and R^{3b} represent T^2-[C(H)=], wherein T^2 is bonded to the C-atom to which the group R^2 is attached;

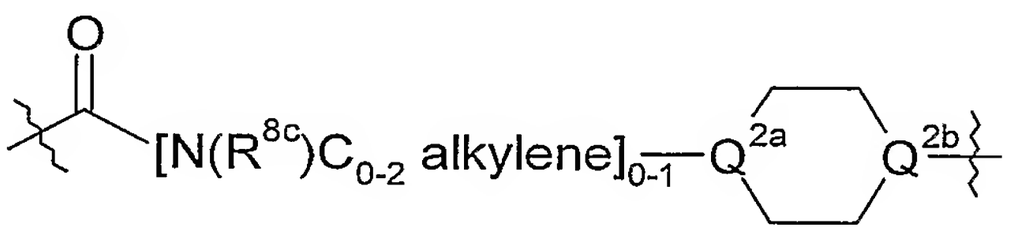
T^1 and T^2 independently represent O, S, N(H) or N(C_{1-4} alkyl);

G represents

(a) -C(O)N(R^{8a})-[CH(C(O)R^9)]$_{0-1}$-C_{0-3} alkylene-(Q^1)$_a$-,

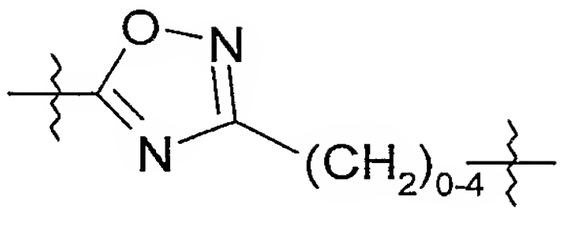
(b) -C(O)N(R^{8b})-C_{2-3} alkenylene-(Q^1)$_a$-,

(c)



, or

(d)



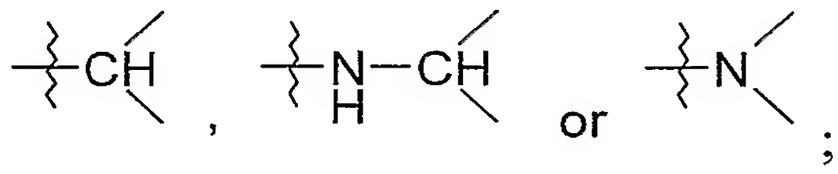
;

R^9 represents H or a 5- to 10-membered aromatic heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one or more nitrogen atoms, which heterocyclic group is optionally substituted by one or more substituents selected from halo and C_{1-6} alkyl;

Q^1 represents O, NR^{10a}, $[N(H)]_{0-1}C(O)$-C_{0-2} alkylene, C(O)NHNHC(O), or -N=C(R^{10b})-;

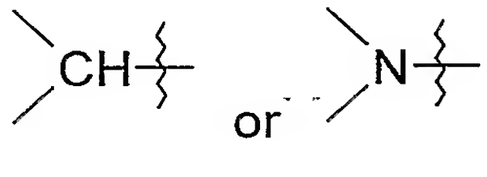
a represents 0 or 1;

Q^{2a} represents



;

Q^{2b} represents



;

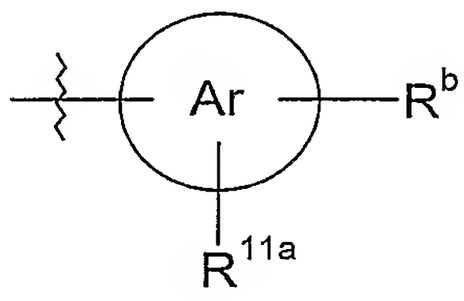
L represents

(a) C_{0-6} alkylene-R^a,

(b) C_{0-2} alkylene-CH=CH-C_{0-2} alkylene-R^a,

(c) C_{0-2} alkylene-C≡C-C_{0-2} alkylene-R^a,

(d)



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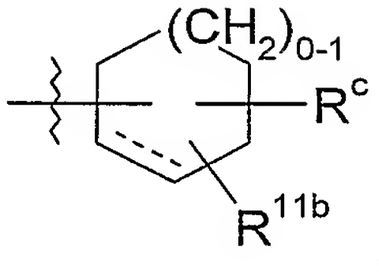
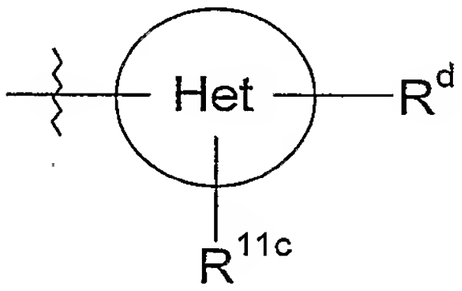
(e)



wherein the dashed line represents an optional double bond, or

(f)



;

Ar represents phenyl or naphthyl;

Het represents a 5- to 10-membered heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one or more nitrogen atoms;

R^{11a} represents H or one or more substituents selected from halo, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-4} alkoxy; $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$) and $S(O)_{0-2}R^{12d}$;

R^{11b} and R^{11c} independently represent H or one or more substituents selected from halo, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-4} alkoxy, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$), $S(O)_{0-2}R^{12d}$, =O, =NH, =NOH and =N-CN;

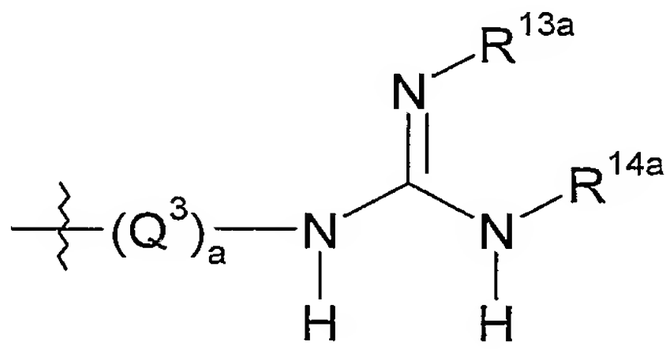
R^{12a} to R^{12c} independently represent H, C_{1-6} alkyl or C_{3-7} cycloalkyl (which latter two groups are optionally substituted by one OH or $N(R^{12e})R^{12f}$ group or by one or more halo atoms);

R^{12d} represents, independently at each occurrence, C_{1-6} alkyl optionally substituted by one OH or $N(R^{12e})R^{12f}$ group or by one or more halo atoms;

R^{12e} and R^{12f} represent, independently at each occurrence, H or C_{1-4} alkyl optionally substituted by one or more halo atoms;

R^a to R^d independently represent

(a)



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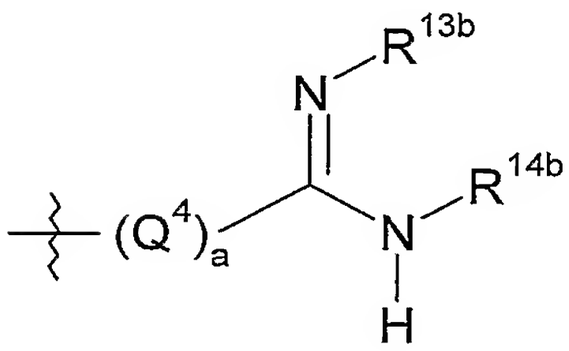
(b)



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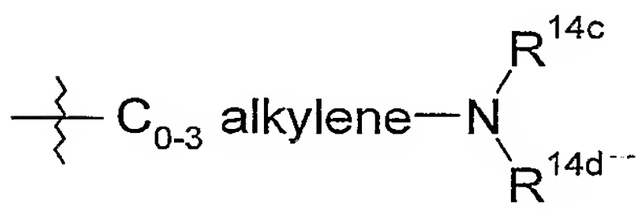
(c)



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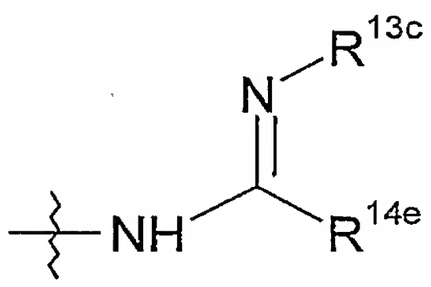
(d)



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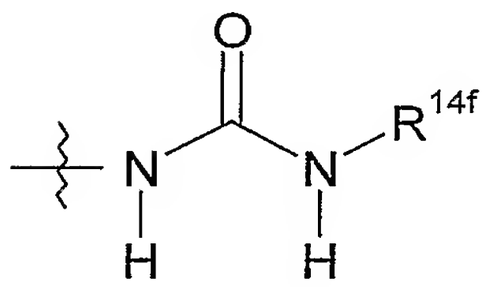
(e)



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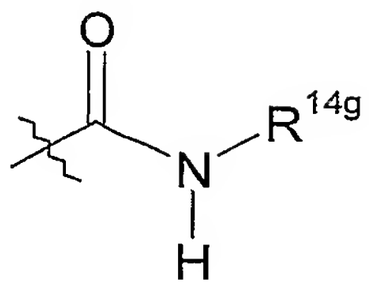
(f)



,

(g) Het^x

or R^b to R^d may also represent H;

Q^3 represents O, $N(R^{10c})$, $S(O)_2$, $S(O)_2NH$, C(O) or -CH=N-;

Q^4 represents O, S or CH_2;

a represents 0 or 1;

Het^x represents a 5- or 6-membered heterocyclic group containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group may be substituted by one or more substituents selected from halo, =O, C_{1-6} alkyl and C_{1-6} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

R^{13a} to R^{13c} independently represent

(a) H,

(b) CN,

(c) NH_2,

(d) OR^{15} or

(e) $C(O)OR^{16}$;

R^{15} represents

(a) H,

(b) C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl,

(c) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and C_{1-6} alkyl, or

(d) C_{1-3} alkyl, which latter group is optionally interrupted by oxygen and is substituted by aryl or -O-aryl;

R^{16} represents

(a) C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, which latter three groups are optionally interrupted by one or more oxygen atoms, or

(b) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and C_{1-6} alkyl, or

(c) C_{1-3} alkyl, which latter group is optionally interrupted by oxygen and is substituted by aryl or -O-aryl;

R^{8a} to R^{8c}, R^{10a} to R^{10c} and R^{14a} to R^{14g} independently represent

(a) H or

(b) C_{1-4} alkyl (which latter group is optionally substituted by one or more substituents selected from halo and OH),

or R^{14a} and R^{14b} independently represent $C(O)O$-C_{1-6} alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or R^{14c} represents

(a) C_{1-4} alkyl substituted by C_{3-7} cycloalkyl or aryl,

(b) C_{3-7} cycloalkyl,

(c) $C(O)O$-C_{1-6} alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

(d) $C(O)C_{1-6}$ alkyl,

(e) $C(O)N(H)$-C_{1-6} alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms) or

(f) $S(O)_2$-C_{1-6} alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or R^{14c} and R^{14d} together represent C_{3-6} *n*-alkylene optionally interrupted by O, S, N(H) or N(C_{1-4} alkyl) and/or substituted by one or more C_{1-4} alkyl groups;

each aryl independently represents a C_{6-10} carbocyclic aromatic group, which group may comprise either one or two rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkoxy, C(O)OH, C(O)O-C_{1-6} alkyl, phenyl (which latter group is optionally substituted by halo) and Het^7),

(d) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl (which latter group is optionally substituted by halo) and Het^8),

(e) OR^{17a},

(f) $S(O)_pR^{17b}$,

(g) $S(O)_2N(R^{17c})(R^{17d})$,

(h) $N(R^{17e})S(O)_2R^{17f}$,

(i) $N(R^{17g})(R^{17h})$,

(j) B^5-C(O)-B^6-R^{17i},

(k) phenyl (which latter group is optionally substituted by halo),

(l) Het^9 and

(m) $Si(R^{18a})(R^{18b})(R^{18c})$;

R^{17a} to R^{17i} independently represent, at each occurrence,

(a) H,

(b) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkoxy, phenyl (which latter group is optionally substituted by halo) and Het^{10}),

(c) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl (which latter group is optionally substituted by halo) and Het^{11}),

(d) phenyl (which latter group is optionally substituted by halo) or

(e) Het^{12},

provided that R^{17b} does not represent H when p is 1 or 2;

Het^{1} to Het^{12} independently represent 4- to 14-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkoxy, C(O)OH, C(O)O-C_{1-6} alkyl, phenyl (which latter group is optionally substituted by halo) and Het^{a}),

(d) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl (which latter group is optionally substituted by halo) and Het^{b}),

(e) =O,

(f) OR^{19a},

(g) $S(O)_qR^{19b}$,

(h) $S(O)_2N(R^{19c})(R^{19d})$,

(i) $N(R^{19e})S(O)_2R^{19f}$,

(j) $N(R^{19g})(R^{19h})$,

(k) B^{7}-C(O)-B^{8}-R^{19i},

(l) phenyl (which latter group is optionally substituted by halo),

(m) Het^c and

(n) $Si(R^{20a})(R^{20b})(R^{20c})$;

R^{19a} to R^{19i} independently represent, at each occurrence,

(a) H,

(b) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkoxy, phenyl (which latter group is optionally substituted by halo) and Het^d),

(c) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl (which latter group is optionally substituted by halo) and Het^e),

(d) phenyl (which latter group is optionally substituted by halo) or

(e) Het^f,

provided that R^{19b} does not represent H when q is 1 or 2;

Het^a to Het^f independently represent 5- or 6-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may be substituted by one or more substituents selected from halo, =O and C_{1-6} alkyl;

B^1 to B^8 independently represent a direct bond, O, S or NH;

n, p and q independently represent 0, 1 or 2;

R^{18a}, R^{18b}, R^{18c}, R^{20a}, R^{20b} and R^{20c} independently represent C_{1-6} alkyl or phenyl (which latter group is optionally substituted by halo or C_{1-4} alkyl);

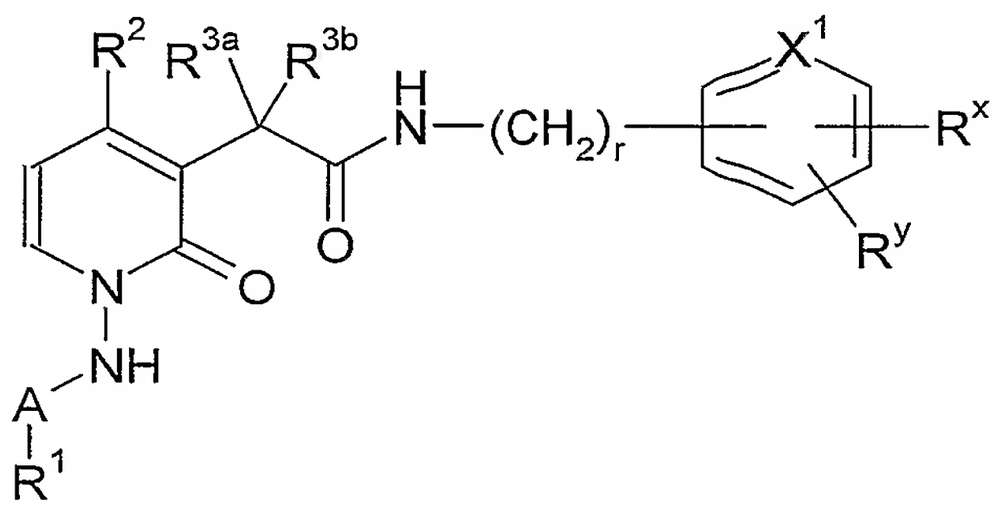
unless otherwise specified

(i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkylene and alkenylene groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms, and

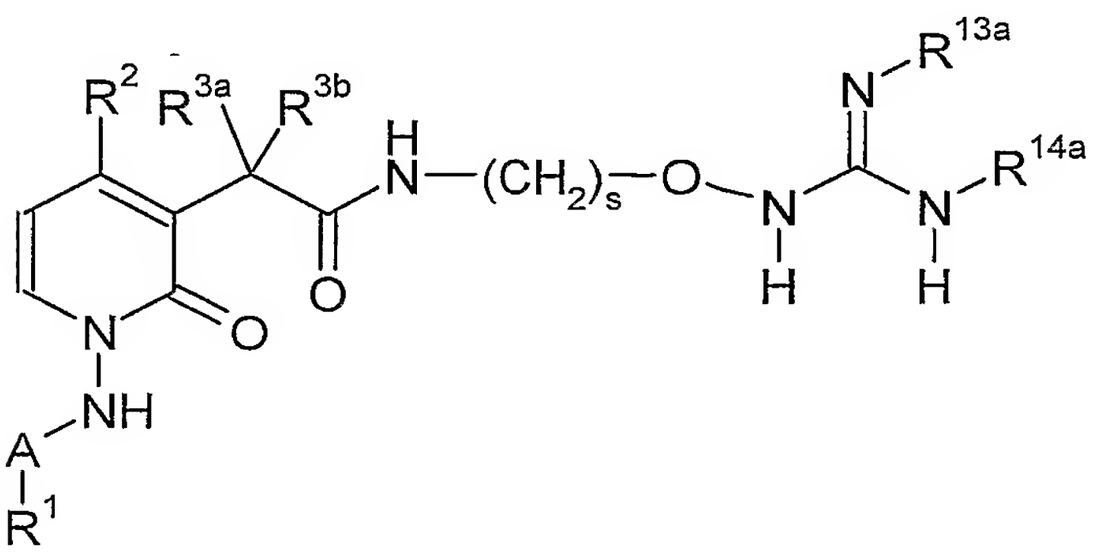
(ii) cycloalkyl and cycloalkenyl groups may comprise one or two rings and may additionally be ring-fused to one or two phenyl groups;

or a pharmaceutically-acceptable derivative thereof.

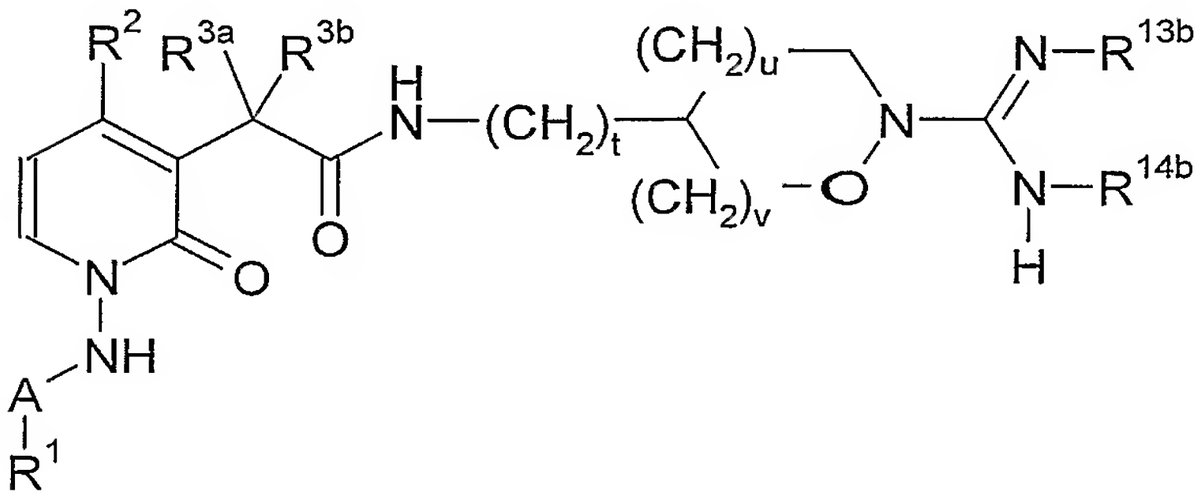
2. A compound as claimed in Claim 1, which is a compound of formula Ic, Id or Ie,



Ic



Id



Ie

wherein X^1 represents CH or N;

when X^1 represents CH

(a) R^x represents R^b as defined in Claim 1, and

(b) R^y represents R^{11a} as defined in Claim 1;

when X^1 represents N

(a) R^x represents R^d as defined in Claim 1, and

(b) R^y represents R^{11c} as defined in Claim 1;

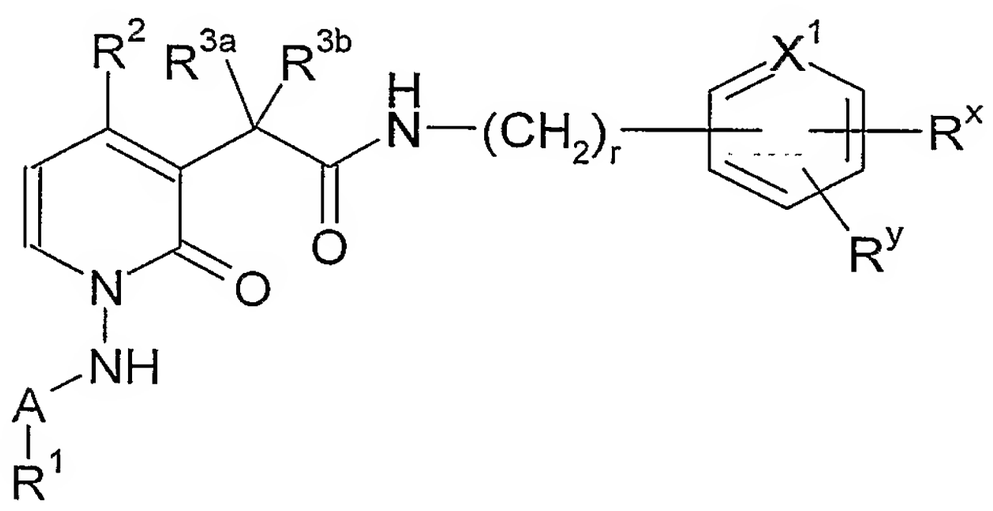
r represents 1 to 3;

s represents 2 to 4;

t represents 1 to 3;

u and v independently represent 0 to 2, the sum of u and v being 1 or 2; and R^1, R^2, R^{3a}, R^{3b}, R^{11a}, R^{11c}, R^{13a}, R^{13b}, R^{14a}, R^{14b}, R^b, R^d and A are as defined in Claim 1.

3. A compound as claimed in Claim 2 which is a compound of formula Ic,



Ic

wherein

A represents $CH(CH_3)CH_2$ (in which latter group the $CH(CH_3)$ unit is attached to R^1) or CH_2, $(CH_2)_2$ or CF_2CH_2 (in which latter group the CF_2 unit is attached to R^1);

R^1 represents

(a) isopropyl or *tert*-butyl,

(b) cyclopentyl, cyclohexyl or bicyclo[2.2.1]hept-5-ene,

(c) phenyl optionally substituted by one or two substituents selected from halo, CN, methyl, CF_3, methoxy, OCF_3, phenoxy, morpholin-4-yl or O-CH_2-(2-chlorothiazol-5-yl),

(d) imidazolyl optionally substituted by one to three substituents selected from Cl, methyl and phenyl,

(e) isoxazolyl optionally substituted by one or two substituents selected from methyl, phenyl and 2-thienyl,

(f) thiazolyl optionally substituted by one or two methyl groups,

(g) thienyl optionally substituted by Cl or pyridinyl,

(h) pyrazolyl optionally substituted by one to three substituents selected from Cl, methyl, ethyl, phenyl and morpholin-4-yl,

(i) pyrrolyl optionally substituted by one to three substituents selected from methyl, $S(O)_2$-phenyl, C(O)-phenyl and 1,3,4-triazol-1-yl,

(j) pyridinyl optionally substituted by OH, methoxy or morpholin-4-yl, and optionally in the form of an *N*-oxide,

(k) pyridonyl,

(l) pyrazinyl,

(m) benzodioxolyl optionally substituted by halo,

(n) benzomorpholinyl optionally substituted by methyl;

(o) 2,1,3-benzoxadiazolyl,

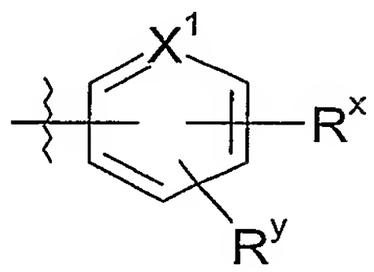
(p) 2,3-dihydrobenzofuranyl or

(q) quinolinyl;

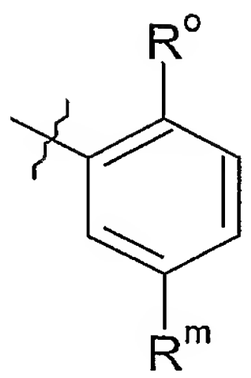
R^5 and R^6 both represent H;

r represents 1;

the group



represents



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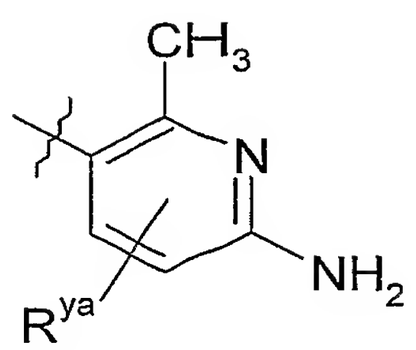


;

R^o represents H, F, Cl, OH, methyl, tetrazol-1-yl, $OCH_2C(O)N(H)R^{12b}$ or $CH_2N(H)R^{14c}$;

R^{12b} represents H or C_{1-3} alkyl optionally substituted by $N(CH_3)_2$;

R^{14c} represents C(O)O-*tert*-butyl, H, ethyl, CH_2CF_3 or cyclopentyl;

R^m represents H, methyl, CF_3, methoxy, F or Cl; and

R^{ya} represents H or methyl.

4. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 3, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

5. A compound as defined in any one of Claims 1 to 3, or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.

6. The use of a compound as defined in any one of Claims 1 to 3, or a pharmaceutically acceptable derivative thereof, as an active ingredient for the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is beneficial.

7. A method of treatment of a condition where inhibition of thrombin is beneficial, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 3, or a

pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

8. A process for the preparation of a compound of formula I as defined in Claim 1, which comprises:

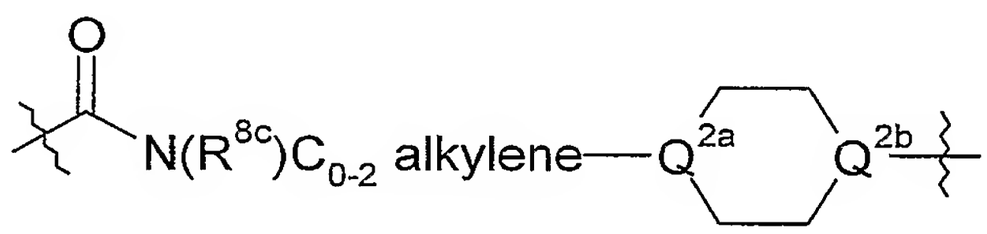
(a) for compounds of formula I in which the group G represents

(i) $C(O)N(R^{8a})$-$[CH(C(O)R^{9})]_{0-1}$-C_{0-3} alkylene-$(Q^{1})_{a}$-,

(ii) $C(O)N(R^{8b})$-C_{2-3} alkenylene-$(Q^{1})_{a}$-,

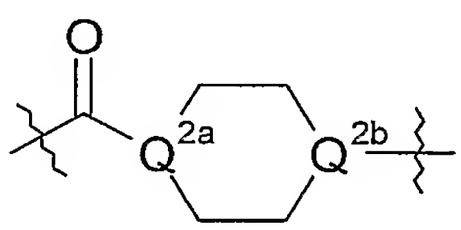
(iii) $C(O)N(R^{8b})$-C_{2-3} alkynylene-$(Q^{1})_{a}$-,

(iv)



or

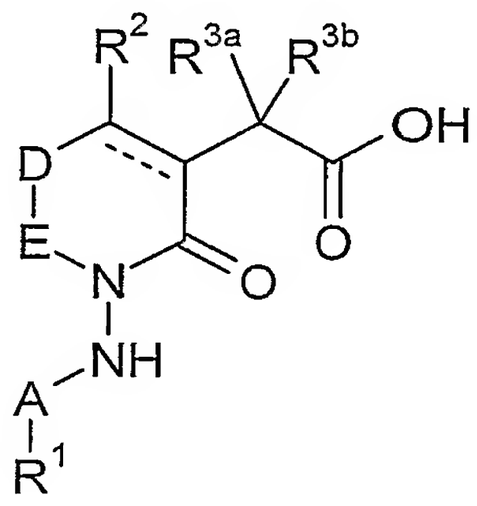
(v)



,

wherein Q^{2a} represents N or NHCH,

coupling of a compound of formula II,



II

wherein the dashed line, R^{1}, R^{2}, R^{3a}, R^{3b}, A, D and E are as defined in Claim 1, with a compound of formula III,

$H\text{-}G^{a}\text{-}L$ III

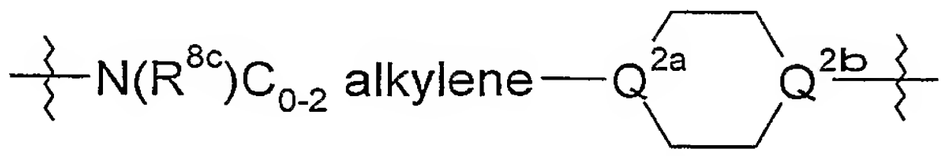
wherein L is as defined in Claim 1 and G^{a} represents

(i) $-N(R^{8a})-[CH(C(O)R^9)]_{0-1}-C_{0-3}$ alkylene-$(Q^1)_a$-,

(ii) $-N(R^{8b})-C_{2-3}$ alkenylene-$(Q^1)_a$-,

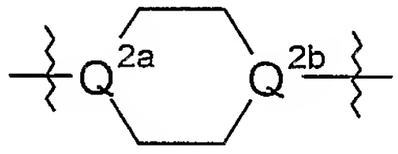
(iii) $-N(R^{8b})-C_{2-3}$ alkynylene-$(Q^1)_a$-,

(iv)



or

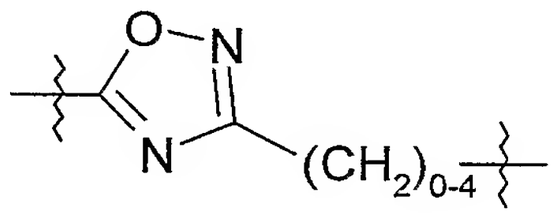
(v)



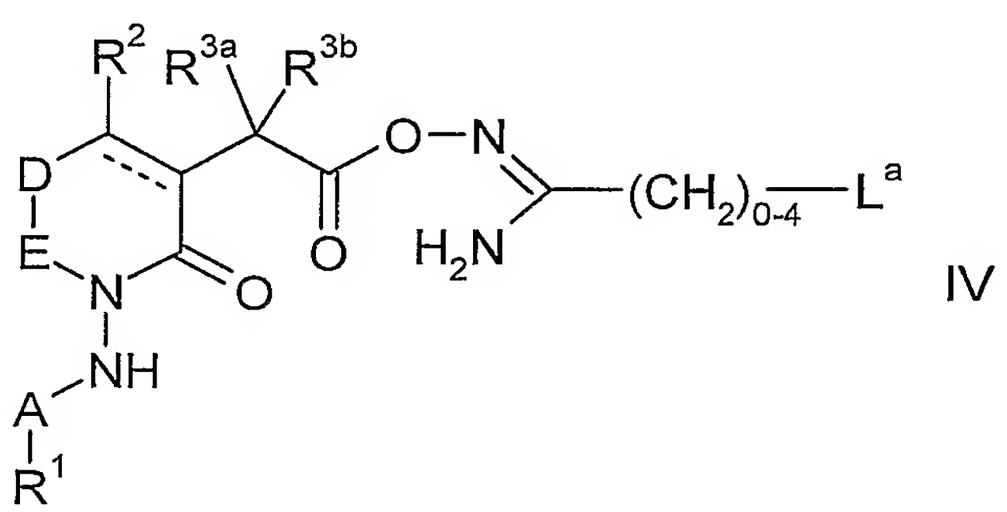
,

wherein Q^{2a} represents N or NHCH and R^{8a}, R^{8b}, R^{8c}, R^9, Q^1, Q^{2b} and a are as defined in Claim 1;

(b) for compounds of formula I in which G represents



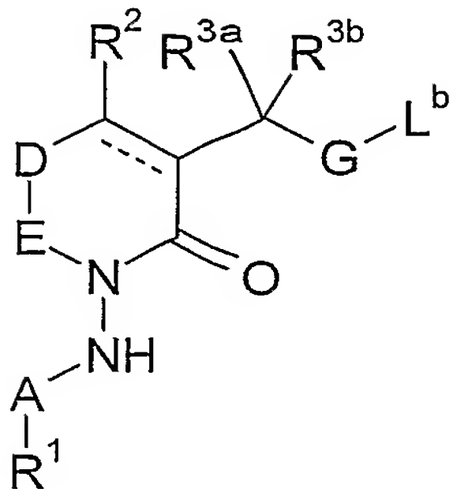
and L represents L^a, which latter group represents L as defined in Claim 1, except that it does not represent C_0 alkylene-R^a, cyclisation of a compound of formula IV,



IV

wherein L^a is as defined above and the dashed line, R^1, R^2, R^{3a}, R^{3b}, A, D and E are as defined in Claim 1;

(c) for compounds of formula I in which R^a, R^b, R^c or R^d represents $-C(=NH)NH_2$, $-C(=NNH_2)NH_2$ or $-C(=NOH)NH_2$, reaction of a compound of formula V,



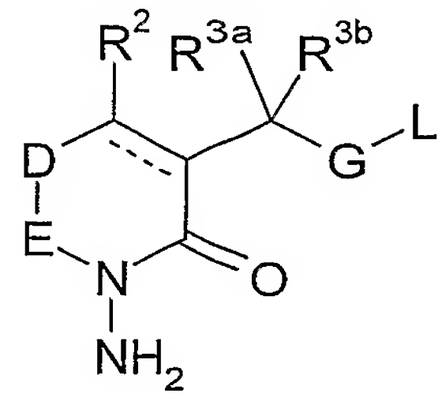
V

wherein L^b represents L as defined in Claim 1, except that R^a, R^b, R^c or R^d (as appropriate) is replaced by a cyano or -C(=NH)O-C_{1-4} alkyl group, and the dashed line, R^1, R^2, R^{3a}, R^{3b}, A, D, E and G are as defined in Claim 1, with a suitable source of ammonia, hydrazine or hydroxylamine;

(d) for compounds of formula I in which R^{13a}, R^{13b} or R^{13c} represents H, deprotection of a corresponding compound of formula I in which R^{13a}, R^{13b} or R^{13c} (as appropriate) represents C(O)O-CH_2aryl;

(e) for compounds of formula I in which R^{14c} represents H, deprotection of a corresponding compound of formula I in which R^{14c} represents C(O)O-C_{1-6} alkyl;

(f) reaction of a compound of formula VI,



VI

wherein the dashed line, R^2, R^{3a}, R^{3b}, A, D, E, G and L are as defined in Claim 1, with a compound of formula VII,

$$R^1\text{-A-}Lg^1 \qquad \text{VII}$$

wherein Lg^1 represents a leaving group and R^1 and A are as defined in Claim 1;

(g) for compounds of formula I in which A represents C(O)NH, reaction of a compound of formula VI, as defined above, with a compound of formula VIII,

R^1-N=C=O VIII

wherein R^1 is as defined in Claim 1;

(h) for compounds of formula I in which A represents C_{1-6} alkylene, reaction of a compound of formula VI, as defined above, with a compound of formula IX,

R^1-C_{0-5} alkylene-CHO IX

wherein R^1 is as defined in Claim 1, followed by reduction in the presence of a reducing agent; or

(i) for compounds of formula I in which R^a, R^b, R^c or R^d represents -C(=NCN)NH_2, reaction of a corresponding compound of formula I in which R^a, R^b, R^c or R^d, respectively, represents -C(=NH)NH_2 with cyanogen bromide.

9. A compound of formula II, as defined in Claim 8, or a protected derivative thereof.

10. A compound of formula IV, as defined in Claim 8, or a protected derivative thereof.

11. A compound of formula VI, as defined in Claim 8, or a protected derivative thereof.